IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
Audrey GODDARD, *et al.*	)	Art Unit: 1646
Application Serial No. 09/902,713	)	Confirmation No: 1320
Filed: July 10, 2001	)	Attorney's Docket No. 39780-1618 P2C34
For: **ANTIBODIES TO PRO269 POLYPEPTIDES**	)	**Customer No. 77845**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 32613-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Actions mailed on November 7, 2007 and November 30, 2007. A Notice of Appeal was filed therein on February 20, 2008. A request for a one-month extension of time is requested herewith. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The following constitutes the Appellants' Brief on Appeal.

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 2001, at Reel 011964 and Frame 0181. The present application is a continuation of U.S. Serial No. 09/665,350.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to antibodies to a polypeptide referred to herein as "PRO269." There exist two related patent applications, (1) U.S. Patent Application Serial No. 09/907,841, now Patent No. 7, 033, 825, issued 04-25-2006 (containing claims directed to nucleic acids encoding PRO269 polypeptides), and (2) U.S. Patent Application Serial No. 09/904,766, filed November 12, 2001 (containing claims directed to PRO269 polypeptides). Related U.S. Patent Application Serial No. 09/904,766 application is also under final rejection by the same Examiner, and based upon the same outstanding rejections, is being appealed independently and concurrently herewith. Although there exist several applications directed to the "gene amplification" utility, in general, under Appeal, none of these are related to PRO269 molecules or antibodies binding to it.

III. STATUS OF CLAIMS

Claims 39-43 are in this application.

Claims 1-38 and 44 have been canceled.

Claims 39-43 stand rejected and Appellants appeal the rejection of these claims.

IV. STATUS OF AMENDMENTS

A summary of the prosecution history for this case is as follows:

Previously, two Final Office Actions were mailed on September 27, 2006 and October 13, 2006, and a Response and a Notice of Appeal was filed March 13, 2007. An Advisory Action was mailed April 2, 2007. An Appeal Brief was subsequently filed on August 13, 2007. The finality of the rejection was then withdrawn by the Examiner in the Final Office Actions mailed on November 7, 2007 and November 30, 2007. A Notice of Appeal was filed on February 20, 2008.

No claim amendments have been submitted after the Response mailed March 13, 2007.

A copy of the rejected claims in the present Appeal is provided in the Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 96 (Claim 39). The invention is further directed to an antibody that specifically binds to the polypeptide of SEQ ID NO: 96 which is a monoclonal antibody, a humanized antibody or an antibody fragment. (Claims 40, 41 and 42, respectively). The invention is further directed to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 96 which is labeled. (Claim 43). The PRO269 gene was shown for the first time in the present application to be significantly amplified, ranging from **2.0-3.5 fold amplification in eight primary lung tumors or cell lines** as compared to normal, non-cancerous human tissue controls (Example 92, in the specification at page 222, line 26, to page 235, line 3).

Support for the preparation and uses of antibodies are found throughout the specification, including, for example, pages 199-203. The preparation of antibodies is described in Example 57 (pages 199-200), while Example 59 (pages 200-201) describes the use of the antibodies for purifying the polypeptides to which they bind. Isolated antibodies are defined in the specification at page 76, line 38, to page 77, line 1. Support for monoclonal antibodies is found in the specification at, for example, page 73, lines 31-33. Support for humanized antibodies is found in the specification at, for example, page 141, line 15, to page 142, line 16. Support for antibody fragments is found in the specification at, for example, page 75, line 38 onwards to page 76, line 19. Support for labeled antibodies is found in the specification at, for example, page 77, lines 9-12.

The amino acid sequence of the native "PRO269" polypeptide and the nucleic acid sequence encoding this polypeptide (referred to in the present application as "DNA35705") are shown in the present specification as SEQ ID NOs: 96 and 95, respectively, and in Figures 36 and 35, described on page 60, lines 18-22. The full-length PRO269 polypeptide having the amino acid sequence of SEQ ID NO:96 is described in the specification at, for example, on page 12, line 30 to page 13, line 1, page 40, lines 1-11, page 103, lines 4-12, in Figure 36 and in SEQ ID NO:96 and the isolation of cDNA clones encoding PRO269 of SEQ ID NO:95 is described in Example 15, page xx of the specification, as well as in Figure 35 and in SEQ ID NO:95.

Finally, Example 92, in the specification at page 222, line 26, to page 235, line 3, sets forth a 'Gene Amplification assay' which shows that the PRO269 gene is amplified in the genome of certain human lung cancers (see Table 9, page 230). The profiles of various primary lung tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 227 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 39-43 satisfy the utility/ enablement requirement under 35 U.S.C. §§101/112, first paragraph.

VII. ARGUMENTS

Summary of the Arguments

Issue 1: Utility/ Enablement

Appellants rely upon the gene amplification data of the PRO269 gene for patentable utility of the PRO269 polypeptides and the antibodies thereof. This data is clearly disclosed in the instant specification in Example 92 which discloses that the gene encoding PRO269 showed significant amplification, ranging from **2.0-3.5 fold amplification in eight primary lung tumors or cell lines**.

Appellants have submitted, in their Response filed March 31, 2003, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of colon and lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Appellants have also submitted, in their Responses filed November 3, 2004, and August 21, 2006, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression.

Appellants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration (made of record in Appellants' Response filed October 16, 2003) and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed May 21, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level). Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO269 is useful as a diagnostic tool for detecting lung tumors.

As the Examiner no longer questions whether mRNA levels are not predictive of polypeptide levels, the evidence presented by Appellants support that gene amplification correlates with the increased mRNA expression. Based on the **2.0-3.5 fold amplification in eight primary lung tumors or cell lines**, one of ordinary skill would find it credible that the claimed anti-PRO269 antibodies would have utility as markers for the diagnosis of lung tumors, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Further, Appellants submit that one of ordinary skill in the art would know how to make and use the recited antibodies for the diagnosis of lung cancers without any undue experimentation, based on the detailed teachings in the specification.

Accordingly, this utility and enablement rejections under 35 U.S.C. §§101 and 112, first paragraph should be withdrawn.

Response to Rejections

ISSUE 1. Claims 39-43 are Supported by a Credible, Specific and Substantial Asserted Utility, and Thus, Meet the Utility Requirement of 35 U.S.C. §§101/112, First Paragraph

The sole basis for the Examiner's rejection of Claims 39-43 under this section is that the data presented in Example 92 of the present specification is allegedly insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. §101 for the presently claimed subject matter.

Claims 39-43 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Appellants strongly disagree and, therefore, respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. §101

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title. (Emphasis added).

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent Applicant disclose a "substantial utility" for his or her invention, *i.e.*, a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

Later, in *Nelson v. Bowler,*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Appellant's assertion of utility creates a presumption of utility that will be sufficient

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[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11,12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services

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[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied,* 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. Proper Application of the Legal Standard

Appellants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

Appellants respectfully submit that the data presented in Example 92 starting on page 222 of the specification of the specification and the cumulative evidence of record, which underlies the current dispute, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Patentable utility for the PRO269 polypeptides and the antibodies thereof is based upon the gene amplification data for the gene encoding the PRO269 polypeptide. Example 92 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art

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[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 230 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 227). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control and also, no-template controls (pages 222-234). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on pages 222-223. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on. Using this PCR-based assay, Appellants showed that the gene encoding for PRO269 was amplified, that is, it showed approximately 1.04-1.60 ΔCt units which corresponds to **2.00-3.5-fold** amplification in eight primary lung tumors or cell lines.

Appellants submitted a Declaration by Dr. Audrey Goddard which provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.
> (Emphasis added).

Accordingly, the **2.00-3.5-fold** amplification in eight primary lung tumors or cell lines would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration. As any skilled artisan in the field of oncology would easily appreciate that this gene is a good candidate marker for diagnosing lung tumors and would

clearly find utility for the PRO269 gene as a diagnostic for lung cancer or for diagnosing individuals at risk for developing lung cancer.

The Examiner has asserted that "[t]he basis of the maintained rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels." (Page 3 of the Final Office Action November 30, 2007). The Examiner has also alleged, based on Sen *et al.*, and Hittelman *et al.* that the observed gene amplification was not corrected for aneuploidy. The Examiner has also asserted it is not clear whether PRO269 is amplified in cancerous lung tissue more than in damaged lung tissue. (Page 4 of the Final Office Action November 30, 2007)

Appellants respectfully disagree and submit that their gene amplification data was not due to aneuploidy. Appellants had submitted the Ashkenazi Declaration to show that "detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy." Regarding Sen *et al.* and Hittelman *et al.*, Appellants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer. These cited references in fact support the Appellants' position that PRO269 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in colon cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged colon lesions which may eventually lead to colon cancer. Many articles published around the effective filing date of this application studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of cancer. Based on the well-known art, Appellants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

C. A *prima facie* case of lack of utility has not been established

The Examiner has asserted, based on Pennica *et al.*, Konopka *et al.*, Godbout *et al.*, and Li *et al.* that there is a general lack of correlation between gene amplification and mRNA expression (Pages 4-7 of the Final Office Action mailed November 30, 2007).

As a preliminary matter, Appellants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels or that polypeptide levels can be "accurately predicted." As discussed

above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants submit that Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and mRNA levels. According to the quoted statement from Pennica *et al.*, "WISP-1 gene amplification in human colon and lung tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon and lung tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon and lung tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-

expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Similarly, in Konopka *et al.*, Appellants submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al* ., Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility. Therefore, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels.

The Examiner has asserted that unlike Godbout *et al.*, the instant specification does not teach structure/ function analysis and the Examiner questions whether the level of genomic amplification of DDX1 gene is comparable to that disclosed by PRO269. The Examiner has further asserted that, there is no evidence in the present application that PRO1112 confers growth advantage to the cells. (Page 11 of the Office Action mailed in November 30, 2007)

Regarding the Godbout reference, Appellants respectfully submit that it was never claimed that PRO269 is similar in any way to the DDX1 gene of Godbout *et al.,* they never claimed PRO269 was an RNA helicase or that it confers selective advantage to cell survival; on the other hand, the Godbout reference was submitted to show good correlation between protein levels based upon genomic DNA amplification, which the Examiner clearly agrees with. Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Structure/function data, which the Examiner requests, is not a requirement for the utility requirement. Hence this rejection is improper.

The Examiner has cited Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 7 of the Office Action mailed in November 30, 2007)

Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO269, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold). The PRO269 gene showed significant amplification of **2.00-3.5-fold** amplification in eight primary lung tumors or cell lines, and thus fully meets this standard. It is not surprising that in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Moreover, Appellants add that the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO269, would be expected to show a corresponding increase in transcript expression.

It is "more likely than not" for amplified genes to have increased mRNA

On the contrary, Appellants submit that Example 92 of the specification further discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as lung, colon, breast and other cancers and diagnostic determination of the presence of those cancers" (Emphasis added). Besides, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the corresponding mRNA will also be expressed at an elevated level.

For instance, Appellants presented the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Responses filed November 3, 2004, and August 21,

2006), who collectively teach that in general, for most genes, DNA amplification increases mRNA expression. The results presented by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Appellants further submit that Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly

shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip® arrays in 2004. Clearly, the research community believe that the information obtained from these chips is useful (*i.e.*, that it is more likely than not that the results are informative of protein levels).

Thus, the Examiner appears to disregard the ample evidence provided in the above referenced articles based on misinterpretations of their teachings. Appellants submit that in fact, these articles lend significant support that for an amplified gene, it is more likely than not that the protein will also be overexpressed and would be viewed as reasonable and credible by one of ordinary skill in the art. The "more likely than not" standard is a much lower standard than a "necessary" correlation or "accurate" prediction, and is clearly met in the claimed invention. Moreover, the Examiner has not cited any evidence or advanced any arguments as to why Appellants' statement of overexpression of protein would not be credible. Accordingly, this point is believed to be moot.

Appellants respectfully point out that Hyman *et al.* conducted additional studies of one of the genes found to be amplified, HOXB7, and found "a clinical association between HOXB7

amplification and poor patient prognosis." (Page 6244, col.1 to col.2). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. The Board's attention is also respectfully directed to the final paragraph of Pollack *et al.*, wherein the authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Appellants submit is **not** true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. In support, Appellants respectfully draw the Board's attention to page 2 of the Declaration of Dr. Avi Ashkenazi (submitted with the Response filed October 16, 2003) which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Appellants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is

crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), submitted with the Response filed May 21, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner has asserted that Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of polypeptide expression must be tested empirically. (Page 16 of the Office Action mailed November 30, 2007). Appellants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Appellants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

Appellants have clearly shown that the gene encoding the PRO269 polypeptide is amplified in multiple lung tumors. Therefore, the PRO269 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO2692 gene, that the PRO269 polypeptide is concomitantly overexpressed.

The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna article as experiments involving further characterization of the PRO269 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO269 polypeptide, but the tumors in which the gene encoding PRO269 is amplified. The PRO269 polypeptide and the claimed antibodies which bind it are therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Thus, based on the asserted utility for PRO269 in the diagnosis of selected lung tumors, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO:96 in the present application (see page 12, line 30 to page 13, line 1, page 40, lines 1-11, page 103, lines 4-12), the disclosure of the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO269 protein in the specification (in Examples 57-59), and the disclosure of the gene amplification assay in Example 92, the skilled artisan would know exactly how to make and use the claimed antibodies for the diagnosis of colon and lung cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue'.

Therefore, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 39-43.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed antibodies. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 39-43.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **07-1700** (referencing Attorney's Docket No. **GNE-1618 P2C34**).

Respectfully submitted,

Date: MAY 20, 2008

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IX. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

   A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
   B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
   C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
   D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
   E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon and lung tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
   F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
   G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Hanna *et al.*, "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).

4. Sen *et al.* , Current Opinion in Oncology, 12: 82-88, (2000).

5. Orntoft, T.F., *et al.* Molecular & Cellular Proteomics – 1:37-45 (2002).

6. Hyman, E., *et al.*, "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002).

7. Pollack, J.R., *et al.*, "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).

8. Konopka *et al.*, "Variable Expression of the Translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" *Proc. Natl. Acad. Sci. USA* 83: 4049-52, (1986).

9. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," Proc. Natl. Acad. Sci. USA 83: 4049-52 (1986)

10. Godbout, R., *et al.*, J. Biol. Chem. - 273(33):21161-8 (1998).

11. Li *et al.*, 2006, Oncogene 25: 2628-2635.

12. Hittelman *et al.*, *Ann. N.Y. Acad. Sci.* **952**: 1-12 (2001).

Item 1 was submitted with Appellants' Response filed March 31, 2003, and was considered by the Examiner as indicated in the Final Office action mailed June 25, 2003.

Item 2 was submitted with Appellants' Response filed October 16, 2003, and was considered by the Examiner as indicated in the non-final Office Action mailed January 21, 2004.

Item 3 was submitted with Appellants' Response filed May 21, 2004, and was considered by the Examiner as indicated in the Final Office Action mailed January 13, 2005.

Item 4 was made of record by the Examiner in the Office Action mailed June 25, 2003.

Items 5-7 were submitted with Appellants' Response filed November 3, 2004, and were considered by the Examiner as indicated in the Final Office Action mailed January 13, 2005.

Items 8-9 were made of record by the Examiner in the Office Action mailed January 21, 2004.

Item 10 was submitted with Appellants' Response filed August 21, 2006, and were considered by the Examiner as indicated in the Final Office Action mailed September 27, 2006.

Item 11 was made of record by the Examiner in the Final Office Action mailed October 13, 2006.

Item 12 was made of record by the Examiner in Final Office Actions mailed November 7, 2007 and November 30, 2007.

X. RELATED PROCEEDINGS APPENDIX

None.

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